out at multi-year. In the United States the device is currently approved for bridge to cardiac transplant. And most patients will only be on the device a matter of months. Yes, there are some at years, but it's very few.

In Europe, the device is approved for other things. It's not part of our discussion. But the number of patients multi-year is -- there's some data but it's limited, I think would be a fair way to say. But long term durability: (a) is not an issue today, and; (b) is not an obvious problem right now.

DR. YANCY: Well, the only thing that I would retort with is that the language that's requested does include the phrase long term.

DR. BERMAN: Well, we pointed out that based on the dataset we've been given and based on the dataset that you folks are deliberating about today, there were 30 patients six months or more, 15 one year or more, four two years or more. And so we consider that insufficient to justify the use of long term, especially coupled with Dr. Pina's

concern that there really is no accepted definition within the community of what the term long term means.

So we don't think the data supports it and we don't really know what it means to begin with.

DR. YANCY: And this second question is unrelated, but it's for either of the panel members. It has to do with how the question of relative contraindications was addressed with the original application. Was there any comment about that, was there a statement of concern, did it come up for --

DR. BERMAN: Are you asking questions about the PMA application from which the device was approved for bridge?

DR. YANCY: Yes.

DR. BERMAN: To my knowledge, and I was not the lead reviewer, the matter of relative contraindications was not brought forward by the sponsor. But if that's wrong, i would allow them to correct me.

CHAIRPERSON LASKEY: Dr. Krucoff?

DR. KRUCOFF: A question for Dr. Ahn. I'm actually going to resist asking yo why you showed us a survival curve of age divided by three when in the panel pack you used the example of last digit ID 01 or 2 and try and stay on the serious side of just a lay person understanding where statistics are or are not potentially useful in the application for an extended label.

So I think you did a pretty clear job helping me understand the inability to compare these groups. I guess from my limited statistical educational background, when I see numbers like three patients with a total bilirubin greater than five in one group and zero in the other group, there comes a point where populations in a dataset simply are too small to support any statistical conclusion of any kind, not just as a comparability issue between two groups but as an understanding of what role that particular feature in a treatment have with one another.

So my question is where is the lower limit in a dataset of the ability to support any

kind of statistical conclusion at all about the impact of a treatment?

DR. AHN: Notice that the 87 patients sponsor selected, they are a very heterogenous group, as you indicated. They use seven relative contraindications criteria and for some criteria, there was three patients in the treatment group and none in the control group.

And there isn't -- in the frequency table we -- to compare any sensible -- to have any sense of comparison we like to see more than five observations per cell. In this case, three observations taken from treatment and none from control, that might be an also issue, too.

And also total bilirubin, there one patient from LVAS and none from control. And pulmonary resistance, one from LVAS and none from control and so on.

So it is hard to define what the population might be when we have a very heterogenous characteristic sample.

DR. KRUCOFF: Those numbers are from

table 4-1 which is on page 9 of tab 5A of your panel pack?

DR. AHN: And the reason why I showed the subgroup with age divisible by three or patient ID ending in 01 or 2 is to show that the retrospective psychoanalysis is what we try to avoid as a statistician.

DR. AZIZ: I think the question about long term durability I think is an important question. And I know that, obviously, we've got to focus on the data that was presented here today. But I think it would be fair to say that of all the devices that have been implanted both here and in Europe on a long term basis, I think the data in the sort of 1,077 cases that you said we can look at, I don't think that I'm aware of any device that's malfunctioned. And even though we can't look at the data, I think we do have a general idea that -- I mean,, this device in patients in whom it's been in for more than a year or so has been very durable without, I think, stopping or having a malfunction. So I think there is a sense out there that it is a

good device.

The second thing actually, this is for Dr. Pina, looking at bilirubins per se is just one aspect of liver dysfunction. You know, was any attempt made to look at the enzymes, you know, albumin, OT, PT and you know the other parameters rather than just focusing on bilirubins you could have many reasons for being --

DR. PINA: I think you make an excellent point that some of these patients have a lot of other issues with their liver function and that bilirubin is just one of the many. And, in fact, the paper that addresses the hepatic dysfunction actually addresses cytokine and inflammatory factors as being more predictive. However, we have been given as a relative contraindication the total bilirubin, and that's what we have to focus on.

But I agree with you that it is multifactorial.

DR. BAILEY: Can I just ask for my ignorance, is it reasonable to assume that if you have an improvement, let's say, in pulmonary

pressure or in renal function with the device that that has the same implications as someone who hasn't been on a device and has good function as far as post-transplant survival?

DR. PINA: You know, there's never been a randomized controlled trial that looks at that specifically, but I can tell you clinically if the pressures come down with whatever format and stay down, that the patient will do much better. Early and later, because you have a problem early in the operating room and then you have a problem later. so, yes the answer yes.

And we usually wait, even if we do it with medications or we do it with the device, wait and make sure that they are down and stay down and we do repeated hemodynamic monitoring.

DR. YANCY: Let me just raise one other issue with Dr. Pina. The number of patients on LVAS who went on to transplantation, as you pointed out, was 65 percent. Do you have access to information or maybe I overlooked it in the program material, as to whether or not that group that went on in

transplantation was populated towards one or another contraindication more so than the others, that is amongst the seven, the group that actually went for the transplantation did they reflect a certain profile?

DR. PINA: I have not seen that data, unless Dr. Berman has seen it. No, we have not. It would be an interesting point to see.

DR. LINDENFELD: Not only interesting, I think it's critical. And I think that when we come back to the sponsor, what I would like to see is the table of the relative contraindications. And though I recognize some of the numbers are small, I would like to see how many of each contraindication went onto transplant and what the one year survival was for those.

We're asked to say these are relative contraindications and what we'd like to see is 49 were transplanted, were those all the ones with the high BMI? Was there a much lower percentage of the high PVRs or the high creatinines? And I think that's just a very critical question as we look to

say, okay, if you're not sure, we think it's okay to do this. I think we need to see how many were transplanted and subsequently what the one and two year survival in each of those contraindications. And I recognize some of the groups are one in three, but some are 20/22.

CHAIRPERSON LASKEY: A critical and continued source of confusion this relative contraindication business.

Dr. Ahn, do you find it puzzling that when they did the multivariable analyses, their proportional hazards, that three of the variables that were felt to be relative contraindications, systolic, serum creatinine, total bili were not found to be statistically significant predictors of mortality? What is that telling us, besides confusing us?

DR. AHN: When you have multiple variable and we question, for example, if even though one -- if you have one variable in the model, that variable might be significant. But if you include many variables because of interaction

between the variables, some of the variables may not be significant. So I have not seen -- it might be--

CHAIRPERSON LASKEY: But the three things that failed to survive the test are those on which we're relying a great deal of credence in terms of being relative contraindications. These were important physiological that are meant to provide a definition for this patient population and yet they failed to stand up to the statistical rigor.

DR. BAILEY: I think Dr. Ahn is saying that you have to look at the joint effect of those three variables before you could rule out that they had some impact. Not just look at each individual variable as partial -- have you looked at the joint effect of those three variables?

DR. AHN: No, I did not.

DR. BAILEY: But I mean, another possibility obviously is that, you know, how abnormal or how deficient were those parameters? And if we're just at the margin maybe that's part of the story.

DR. KRUCOFF: Another feature, I don't know if this is really fair to ask Dr. Ahn or maybe we can come back in these multivariable models after lunch, but at least my understanding was that the variable entered in that model was probably the initial creatinine and how many of those patients with elevated creatinine had reversible dysfunction versus not may also impact on whether they survived well or poorly. And again, I don't know if it's fair to ask Dr. Ahn, but my understanding of the parameter entered for that model is just a single creatinine value when the patient was enrolled. But maybe we can come back to it.

DR. AHN: Yes. Right.

CHAIRPERSON LASKEY: Yes, Dr. Somberg?

DR. SOMBERG: Well, just a comment and maybe the FDA reviewers would like to expand upon that. But I'm very concerned with what I hear of a number of questions from our panel suggests that in making a decision we're asking for qualifiers when in actuality we're asked to make an evidentiary determination and it's all based on comparison to

something which has to be a control. If the control was inadequate, how can one ever reach a decision regarding whether parameters may go one way, another, they may change. They have to be compared something and if the control is the 12 patients or the 35 patients, if the control is inadequate and not matched, then almost anything you choose will give you a significant difference and there's been no attempt to try to validate that control with any historic other data, why should we determine anything else?

DR. PINA: I want to respond briefly one more time to Dr. Lindenfeld's concern about the lowering.

We do have data. If you go into page 11 of the sponsor's under tab 5A, they tell us that 12 of 22 of the patients who had the definition of renal dysfunction did in fact go to transplant. But what they don't say and what we've never seen is what was the creatinine at the time of transplant in those patients who have the relative contraindications. And table 4-2 shows that the

serum creatinine level in that group was 3.23 and it gives other parameters, but we don't know individually what happened to those patients. And in a similar fashion with the PA pressure and the PDR if you go into the next tables. But in all fairness, we do know how many went to transplant.

CHAIRPERSON LASKEY: If there are no other questions from the panel, that means we are proceeding at an amazing efficient pace here.

Are you prepared to do your view now? Yes, well we can wait.

So what I'd like to do is to have Drs. Krucoff and Somberg give their reviews and ask questions of the sponsor.

Thank you very much FDA folks.

And after they're through, then we'll break for lunch and we'll come back for the panel queries.

DR. KRUCOFF: You want me to start?

CHAIRPERSON LASKEY: Please. Thank you, sir.

If you have a question for them, you

should invite them to the table, yes.

DR. KRUCOFF: Okay. I do have a few questions.

MS. WOOD: I'm sorry, I need to correct that. You come to the podium to answer the questions, either the FDA or the sponsor.

DR. KRUCOFF: Okay. Sorry. I'll direct my questions.

And I guess I'll leave you guys to decide -- I just want to make sure we're starting on the same page.

Certainly my understanding is that for a requested expansion of an indication that the data presented to support that expanded indication should stand alone. And I realize there are certain reference points including the preclinical testing etcetera that we're not revisiting, but at least the clinical data should stand alone.

And I think it as pretty clearly -- I think Dr. Young specifically said, but I think we all appreciate that this is not a dataset that was built on a prospective hypothesis. That this is

retrospective look driven pretty clearly by the dilemma that we face with patients who are sort of on that edge of are they going to be transplant candidates or not and, obviously, the dilemma of whether to employ a technology at this level and to try and better understand how to employ that technology. So that's my take, and please feel free to correct me if any of this incorrect, but that's sort of the spirit, I guess, of what I heard this morning and took from the packet.

But I do think there's an important thing, and again, Dr. Young, you mentioned that retrospective analyses have guided us in transplantation, in fact in many areas of medicine. But I also have to say that from a trials data, from an evidentiary perspective generally what retrospective analyses have guided us towards are a clearer hypothesis to be prospectively tested. And I think one of my main dilemmas with the dataset today is whether the utility of the data presented is helpful for anything except the eventuation of a useful hypothesis to actually be tested by a

meaningful dataset.

And I think another element here that I've been wrestling with are the simply small numbers in many of these categories. So, obviously, if you have zero patients with a particular feature in both categories, there's no way to analyze that. If we have one patient in one group and zero in other and the one patient dies, that's 100 percent mortality. Again, obviously, statistics don't make any sense. As we get two or three or Dr. Ahn was willing to volunteer five in a cell, for certain kinds of safety analysis I think we obviously go down to those numbers and levels. But I have to say that the numbers of patients who have any evidence in some of the categories that are proposed for this expanded indication worry me greatly and make me very concerned, not only that the groups are comparable the control group, but that any sort of real statistical conclusion on the certainty of an outcome in a group with three people in it in patients this sick just defy understanding.

In section 3A in your marketing history

and then later in section 5A you mentioned your experience outside of the U.S., 644 patients. And I realize nobody's had a chance to review this, but boy I have to say when I see 644 patients from 17 other countries in your experience base, my first thought is what's the data? I mean, you know, where are the patients, how many of those patients also have these relative contraindications and with a little more work would it be possible to collect enough information, perhaps, to actually have some data-based evidence with regard to some of these areas of management dilemma that might provide relative contraindications?

But my presumption from the fact that there's really no detailed data on these 644 non-U.S. patients from 17 other countries other than the survival table in table 4-2 that you present on page 8 of section 5A, that we have no other detail in the panel pack and obviously FDA wouldn't have had a chance to reveal any detail. But do you have any information available to us on the relative contraindications list that you're interested in and

its behavior in any of these 644 non-U.S. patients from 17 other countries?

MR. BRYDEN: Is that a question?

DR. KRUCOFF: Yes, that's a question. And I'm sorry, I don't know who. I think they probably want you to come up so it can be recorded.

MR. BRYDEN: The data from the market implants of the device in many countries, we have data in which we can be confident in survival and in device performance because they are reported and we can audit that. But these were not done as part of the trial and we do not have access to the individual conditions of the patient in any reliable manner.

So the answer would be that aside from device failure or not and survival in the market group, we do not have reliable data.

DR. KRUCOFF: Well, because obviously that represents information that would be nice to have and perhaps in a post-market environment something that could be considered would be collecting such data with your implants, if that was

feasible or logistically possible.

Dr. Ahn, you mentioned an ethical issue with regard to randomizing patients who have these relative contraindications. I just wanted to ask you a little bit.

The way I see this right now our implication is that there are a lot of patients who because of their creatinine or their bilirubin or their age or whatever, may not in fact be considered candidates a VAD or transplantation. And a randomized trial, bagging the logistics for a second, just ethically, that a randomized trial from my perspective would be an opportunity not only to afford those patients support and potential conversion to becoming transplant candidates, but in fact that would be a perfect and highly ethical perspective for a randomized trial. Can you help me understand why that would be unethical?

DR. YOUNG: Yes. That's a critically important point that we've actually grappled with. Ileana spoke about our case series which we published in 25 patients who absolutely clearly had

no business being transplanted on the day that they were listed and received a VAD with the intention of rehabilitating their renal function. Now, in those patients very similar to the control group of patients here, which really were quite ill patients as we looked at, I think the invariability of death was present. And the only hope would be to VAD the patient, improve flows to the kidneys, try to attenuate all the multiple pathophysiologic reasons for the renal insufficiency. And the only way, even with all the progress has been made -- and I noticed Dr. Pina didn't include Natrecor on her list of drugs to use. But even with that, really the only thing we have in our bag that we can pull out is a VAD.

And I believe that with the data that exist today it would be unethical to do a randomized trial on this patient population. And I think instead you have to bite the bullet and make the commitment that you're going to try. But this is huge in heroic sort of therapy.

Now, in that case series where we did

that and, this was looked at by appropriate regulatory purview at our institution, we were able to demonstrate that a significant number of patients did improve to a point where we felt comfortable transporting them. And I think that's pretty solid evidence that you can "get away with it" in many cases. But in sense what I'm bothered by is that we haven't clearly defined this when we're going to actually transplant the patient vis-à-vis when we list the patient and put the ventricular assist device in.

But I would have trouble with a randomized trial of VAD versus no VAD in this kind of patient population.

DR. KRUCOFF: So am I missing something. This kind of population patients who have relative contraindications who presumably under standard care would not get listed or transplanted, i.e., would not be candidates for VAD as currently defined?

DR. YOUNG: Correct. And --

DR. KRUCOFF: And would not get VAD or transplanted? So in a randomized trial you'd really

be affording at least half of them or whatever the percentage randomized, something that they're currently not getting access to?

DR. YOUNG: Well, at many centers.

DR. KRUCOFF: Right.

DR. YOUNG: And this represents the diverse opinion that is out there at many different centers. But for me and at my center I would personally have a great deal of difficulty participating in that kind of trial.

DR. KRUCOFF: Because these patients have an opportunity for a VAD based on the judgment of the doc?

DR. YOUNG: Right. That's correct.

DR. KRUCOFF: Okay.

DR. YOUNG: Fair enough?

DR. KRUCOFF: Thanks.

You know, I think personally I have to take a step back and visualize clearly that there are really two decisions here. One is the decision to put in the VAD or not. And the other is ultimately the decision as to whether the patient is

a candidate for transplant and that the temporal sequence of these is -- in BTT you had to start with the patient is a transplant candidate and then they could be afforded a VAD. Now we're asking the question sort of the reverse way; if the patient might be a transplant candidate, should they be afforded a VAD.

So, Mr. Bryden, you've put a slide up that said it was inappropriate to rely on clinicians bending the rules. And to me what we're really talking about here is maybe less the regulatory side of indications supported by data defining populations in safety and efficacy. We're really talking about the practice of medicine is the judgment in the fuzzy zones that we all deal with in devices. So is the implication of your slide that the practice of medicine is a bad thing?

MR. BRYDEN: I think the implication is that where the regulator or those who advise the regulator are of the view that a VAD would be appropriate in the circumstance, that it should be practical to find the words by which that is

approved rather than apparently prohibiting it but expecting medical profession to avoid the prohibition by making judgments which are outside the rules. That was what was intended by t hat comment and that slide.

With respect to the potential for a randomized trial, we are right now engaged in just the very early stages of a randomized trial. And the randomization is that an approved VAD is the control and the Novacor will be the trial arm and the equivalence of the two is what will be tested by the trial.

What we're saying here is that in this case the overall approval that has already been given for this entire population which includes patients who had these contraindications and were listed, that the result of that does demonstrate that these patients benefitted from that listing and as a result the device was approved for that purpose. But on the advice on a number of commission, including those who are with us today, and reviewing the data and surveying centers that do

a significant share of the transplants in the United States, it was quite clear to us that a significant share of those patients who have the relative contraindications which we tested which were included in our group two, would today if presented at many of those centers not be given a VAD.

At the same time, it is clear that to be within this group at all they are at risk of imminent death. How imminent is imminent, seven days was the average within the control group. That is not, we believe, an indication of something wrong with the control group. It demonstrates an imminent means -- imminent, it doesn't mean sometime in the next two years. It means imminent.

So the fact that these patients today would not be provided within the rules that are available access to the VAD and yet within the trial that was conducted, whatever the inadequacies of the controls as they wee a decade ago, the results were clear that a very substantial share of these, in order of 65 percent, survived 30 days post-transplant. And it is very clear that that group

would not and did not survive long without the device, and yet we do have a structure which unless the publications are wrong, the advice we received are wrong, and the survey of these ten centers are wrong, have a hit or miss opportunity dependent largely on the clinicians at the center deciding to implant because their choice is let this person die soon or give him a VAD even though it's not really it's approved for. We're suggesting that is not appropriate.

And the control group in this case is just as it will be in our prospective randomized trial for destination therapy. It is patients receiving the same therapy but with a different medical characteristic. We have that already. It was developed in a controlled trial under the direction of the FDA and was adequate to allow the approval, which has proven to be in the market substantially borne out in the results post-approval with what was expected in the trial results.

So what we have in front of you is not an exercise in standing of a head of a pin in

statistical theory. It is that we have patients who had these characteristics, who had substantially the same results as other patients who did not have those characteristics. And our question to you is, is it not appropriate to regularize the process by which at all centers if they come to the conclusion that this patient is likely to survive to transplant if given a circulatory assist device, that they be permitted to do so within the rules rather than relying on them to bend them?

DR. KRUCOFF: Presuming you have defined the rules, which is what we're here to talk about?

MR. BRYDEN: Yes, exactly. Absolutely. That we are more than happy to be guided by both the panel's advice and the discussions with the FDA about the specifics of the wording. But it is already an established and intentional process by both the FDA and by CMS that they not practice medicine by telling each clinic exactly what will be the criteria for transplant. So what we're doing, as has been done with the approved destination therapy indication, recognizing that is not up to us

to adopt it or not, it's a fact that it exists and to say the process now demands that recognized transplant centers make these judgments. They're not easy judgment. They're very difficult judgments. But the process that you use today throughout this therapy is to require them to make that judgment. All we're saying is apply that judgment in this case as well.

DR. KRUCOFF: Part of the paradox of the BTT dataset to me is that actually the cohort of patients who you have to analyze with these relative contraindications are the results of doctors making judgments --

MR. BRYDEN: Yes.

DR. KRUCOFF: -- that these are patients who would be good candidates and, in fact, based on the evidence the practice of medicine in that case probably is not a bad way to go. But I don't want to get too stuck in this. t's just that the starting point of the BTT group as a listed group of patients creates a paradox ultimately relative to trying to deal with all the patients who might have

these relative contraindications who doctors might not consider to be potential transplant candidates.

MR. BRYDEN: May I make a very --

DR. KRUCOFF: How you would actually define one group from the other, which is the rub:

MR. BRYDEN: May I make a very brief additional comment? I promise it will be very brief.

The use of a list of any kind as a shortcut to defining a population is a useful means of conducting business because it means having done something once and named it. You can just use that name and it always means the same to everyone, so you don't have to go through the whole process again. But when the name of a list does not connote consistent characteristics over time and from center-to-center, the mere fact that a name is or isn't on the list is not evidence on which a regulatory decision should be based in our view. It is the underlying characteristics that can be demonstrated and checked and tested, and judgment made. But whether the name appeared on a list is

not in itself a medical characteristic.

And I think a very considerable amount of the argumentation that we have heard has been whether people were on a list or they're not on a list. The question is, is there a consistent definition of what put you on the list and if so, you know what these people are. The whole point of this exercise is it is not consistent from center-to-center or over time.

So the fact that you are or aren't on the list is neither a good thing for us nor a bad thing for us. It doesn't really tell you anything. We believe you need to examine the underlying characteristics. And in those, we believe, there is reasonable understanding and ability in the clinics to make those judgments.

DR. KRUCOFF: Well, thanks. Actually that's a very good seque into the characteristics issues and my next point. And I don't have too many more. But the one characteristic that was not only a discussion of today but dialogue in the pack between you and FDA previously is reversibility and

nonreversibility of some of these features. And while you made it clear in one of your responses that you're not asking for an indication for reversal of renal dysfunction or for reversal hepatic insufficiency, I think it's pretty clear again, Dr. Young mentioned today, that whether or not these features abate or improve I believe were his words that some of these features and some of the judgment and some of the practice of medicine element here, and one of the biggest missing pieces to me of a characteristic that might be objectified would be reason or evidence that would support the potential reversibility of features like the creatinine or hepatic dysfunction.

So actually I was going to ask Dr. Young first if it's okay, how important is reversibility? As Warren mentioned, and again I don't want to dig beyond my statistical capabilities, but in the multivariable model when elevated creatinine is not predictive of death, one of the things I start to wonder about is well, maybe that's because in a good number of these patients that creatinine reversed

and when they were actually transplanted, their kidneys worked fine when they're given circulation. And, boy, isn't that a great population to put a VAD in? But where is the parameter, the characteristic of reversibility on at least the reversible -- I'm going to ask you about age and body mass in a second. But on the reversible side, on the bilirubin and the creatinine?

DR. YOUNG: Those are very fair, very appropriate questions and drilled down to some of the challenges that we have when we're trying to gain insight from these kinds of databases, retrospective analyses or not. And I liked the presentation about the age or the digit numbers in my slide set about designing and implementing clinical trials. I use that great and important and distinguishing characteristic of your birthday and what sign you happen to be under. And everybody knows the rather famous analyses that have been done in multiple clinical trials that show that.

And so when you cone down into this very important question, and you're right, I don't think

anybody's suggesting that we want to say that these devices are going to be put in ipso facto to cure these difficulties. It turns out that in fact there were significant changes, and I think I showed a few before.

Do we have the slides? You wanted to PA pressure, creatinine improvement, body mass, etcetera, etcetera were the seven relative exclusion factors. And we do have that I believe for everything but, was it age? Age didn't improve. I don't think we have pulmonary vascular resistance.

DR. KRUCOFF: Did it improve body mass?

DR. YOUNG: Yes. Well, actually, I'll show you. Body mass is interesting. In short term there were some rapid changes that probably were fluid and diureses, but long term there were some changes in both the cachectic and the overweight patients, if we could that up.

There we go.

So here is the resolution of these relative contraindications that were picked. And, again, you know I do respect some of the points Dr.

Pina made. Choosing these relative contraindications is not entirely an exact science, and where to put the cut points is inexact, but we do have some guidance. But here you look at the VAS patients that were transplanted and those that were not transplanted in red, and you see an interesting thing; is for one reason or another many of those that weren't transplanted actually got worse. However, the preponderance of the patients that ended up getting transplanted over time, the creatinines got better. So in the individuals that wee hemodynamically supported and, obviously, this isn't necessarily done in a vacuum, but I believe that you can point towards the VAD improving this. With creatinine there was improvement.

What's the next slide?

Pulmonary systolic pressure. Again, tends to fall in everyone that the VAD goes into, whether or not they ultimately get transplanted. But rarely does the PA pressures go up in these patients. And, again, remember the cut point was systolic PA pressure of 60, as I alluded to here

before. So you can see pretty rapidly you'll effect hemodynamics from a decongestion standpoint. And again as was alluded to earlier, whether this is a change in filling pressures in the left ventricle or a change primarily in pulmonary vascular dynamics, I don't know. Often times we can't sort through that. Many patients will get transplanted who have a fixed element of pulmonary hypertension. But you can see here it does what we hope it to do.

Next slide. The next one. What's the next one? Body mass. Okay.

Here's what I was referring to about body mass index. Now, these are what I would call cachectic patients. And here you can see that in patients who are transplanted there's a couple of various responses here.

Now, body mass going up like this in ten to 20 days I don't think is do to resolution of the cachexy necessarily, but maybe changes in volume status that are relative to the transplant.

These patients here, and again we're getting down to small numbers here and I don't want

to make too much of this, but these patients however out 50 and 80 days probably are becoming rehabilitated. And we also know, not from this dataset but we know from other dataset, that that does happen in a cachectic patient when you can feed them.

Next slide. Oh, this is the body mass index for the ponderace patient. And, again, there's a bit of a scatter here, but you see many individuals that actually drop their weight. Why was that? Was that relief of fluid dynamics and ability to diures the patient as you're improving renal function? I assume much of that was. But there's some substantial reductions in body mass index to the area where you have problems with transplant to the area where patients do much better with transplantation. And long term support has been associated, again, in this database as well as in other databases, with improvement.

Did we go backwards or something? We need to body mass index the large patient. The next one, do we have any others? Bilirubin. Go ahead

another one.

See, this refers to what you were pointing out about few patients with a bilirubin greater than 5 in the entire analysis here. But for what it's worth, the one patient that didn't get transplanted continued to get worse. The two patients that did, did in fact improve that parameter.

And, again, like I said we don't have age data for obvious reasons and we don't have pulmonary vascular resistance because of not getting the follow-up wedge pressures on these patients, also for obvious reasons.

So I think when you look at this dataset, yes, it's flawed. And, yes, it's not what we perhaps would like to have with a big randomized clinical trial answering all these questions. Because there's consistency of data in it and it goes along with other impressions that the clinicians that are dealing with these patients have. And though when you do a multivariable analysis these individuals may might not fall out

because of covariate interactions, it certainly is consistent with the clinical picture that we see in small numbers of patients.

Does that answer the questions.

DR. KRUCOFF: Yes. I guess, Jim, one of the things that since clinically we would frequently use to triage patients who we think might be likely to be reversible in some of these features versus not is their history leading up to the point where you're deciding about a VAD. So if somebody had a normal creatinine, came in finally on a flare of heart failure and was rapidly going downhill and their creatinine went to two or three, I would be much more -- I mean, to me that might be a feature that could be characterized in a patient population as opposed to somebody diabetic hypertension who has a creatinine of three for two years.

DR. YOUNG: Right.

DR. KRUCOFF: Where I'd be much less enthusiastic. And I just feel like we're missing of the common sense that might in fact give us characteristics rather than just judgments for

separating out who in these patients might actually benefit --

DR. YOUNG: No, I completely agree. And that's a whole another issue. Actually where I get most challenged about these decisions are the acute myocardial infarction patient who comes in with cariogenic shock, has arrested. These characteristics of that 25 patient case series that we had. Bomb, you resuscitate and the guy wakes up, you know, and they got creatinine of eight and are on hemodialysis sometimes. And you're standing at the bedside and they got a shot ventricle and they're in shock. And you're saying, you know, what are we going to do? Are we going to say this patient is a heart transplant candidate and list him for transplant and then put a VAD in and make him status 7, blah, blah. Well, that's kind of what that case series did.

But, you know, many of these patients certainly fit that criteria. And if you look at the baseline, the number of arrests prior to getting into the BTT and some of the variables, you know

patients were like that.

You could quibble about where to put the creatinine cutoffs and whatnot --

DR. KRUCOFF: Okay. Let's quibble, because that is on my list. So where did you guys get these cutoffs and they're --

DR. YOUNG: Yes. I tell you, that specific data comes from the curves that were generated out of the cardiac transplant research database which shows that there is a biphasic curve for adverse outcome at the time of transplant is the listing creatinine was above 2.5. That's just where the curve break happened to occur, and that was the most recent and the largest data analysis that we had.

And then also when you query transplant physicians and surgeons, you know, where do they put the mark where they raise the eyebrows, generally it's a creatinine clearance of below 50 and really get concerned at a creatinine clearance less than 30. And most of the creatinine clearances are calculated from the Crockroft-Gault equation. And

when you get down into the less than 50 range, is at that 2.5 above, 3, 3.5 and above generally gets you down into that 30 cc less.

So even though I understand the panel's a little queasy about how we sat down and actually picked these, these are criteria that people talk about. There is evidence supporting the number. And interestingly enough, with things like pulmonary artery pressures, obesity and whatnot, there are some insurance carriers that have specifically chosen these same numbers as well as we outlined.

DR. KRUCOFF: So how do you reconcile that with the fact that in your own multivariable model and these data it is not a meaningful cut point?

DR. YOUNG: Well, the multivariable data of this particular, the BTT effort with the stratification, I think this is a numbers and an interaction problem where from a mathematical standpoint we have difficulty account for all of these interactions with the small number of patients that we have. And I'm bothered to some extent, but

I think less bothered than by some others.

DR. KRUCOFF: Except that that's what you're asking for for an indication based on this dataset.

DR. YOUNG: Well, what we're asking for is an indication that if a clinician believes that a patient or expects that a patient's parameters will improve, and we've given some specific parameters if those are the ones that people want to focus on, to a point where they would be willing to accept an organ the day it was offered. The issue again is practice and what happens. and again like those patients that a VAD was put in with renal insufficiency and were listed for transplant, if we got an offer for an organ that day or shortly thereafter, it would be declined. And that is the practice that occurs. It would be declined until parameters were met such as the creatinine drops, the creatinine clearance goes up, pulmonary artery pressures come down until we believe that satisfactory marks have been made. And that, in fact, is the essence of the bridge to a bridge, if

you will. Bridging to the bridge to transplant. Terminology is a little problematic here.

DR. KRUCOFF: Actually, if I can keep you here for a second, Jim, tell me about the nonreversible. Tell me about age, where is the rationale for elevated age at a relative contraindicated level.

DR. YOUNG: Yes.

DR. KRUCOFF: And the decision to implant or an indication for a VAD?

DR. YOUNG: This is perhaps the toughest issue and the most contentious issue, and drive perhaps by the question of age being the primary determine of whether a patient should go the transplant route or a destination therapy route.

If in fact you delve down into all of the databases, age is a consistent marker of less good, if you will to use a nonstatistical term, less good outcomes after transplantation. Now, I'm a strong believer in the relevancy of age. I mean, the oldest patient that we've transplanted was 74 at the time of transplant and was doing quite well.

And so picking a specific age is harder for me to do than many others in the community. And I have to admit I'm in the minority on the age question.

Some people in some programs will say ipso facto, age greater than 60 or age greater than 65, or age greater than 70 makes that patient not a transplant candidate, makes that patient perhaps somebody that destination therapy might be considered in.

Nonetheless, the age mark that was picked, again, was based on several different analyses which show at the elbows at the curve where these changes are occurring. Not all of the databases show the same age. I am, you know, the first to admit that.

And, again, when we look at our own personal experience at the clinic we have very good outcomes with older patients. So in fact if I were to review the contraindications, age would rarely be on that list for any given patient. And my concern would be focused on pulmonary hypertension and renal

insufficiency.

DR. KRUCOFF: Okay. So really we're back to the fact that these are all relative contraindications that in certain medical centers and the discretion of certain physicians you're going to say I think this person is going to do well, and you probably would go to whatever measures would best support the person, including putting a VAD in, if you have the conviction that despite the presence of relative contraindication the overall sense is this patient will probably be a good transplant candidate? Is that where something like age would come in your --

DR. YOUNG: Yes, I think that's a very fair characterization. And, what we have with this analyses is a pretty doggone good evidence base, though flawed. Certainly one of the largest ventricular assist device databases to do that and with varied in it this inherent comparison of those with versus those without these relative contraindications, and then juxtaposed again I'm the first to admit that the control base has flaws with

it. But it's right now I think the best that we can get with this type of questioning and this type of patient population.

DR. KRUCOFF: Well, up until that last phrase, "the best that we can get," I'm actually going to go beyond. I think we have spent a lot of time talking about the comparative issues. And let me just shift to one question about safety. Your slide 34, which had all the various adverse outcomes and the wide confidence intervals, some apparently higher values than others.

DR. YOUNG: Right.

DR. KRUCOFF: Is there any plot that you have available or perhaps by this afternoon could make available on the safety side relative to the timing of some of these events? How many of them cluster very early versus how many of them become issues only in later time periods after three months or six months, or a year, and then again realizing that there are a very few number of patients who have gone longer than that?

DR. YOUNG: Yes, yes. No, we do have

that information. And you're right, some of the events cluster up front and then they taper down with time. As a matter of fact, they were ahead of us, adverse events right there based on the time period, two to six, seven to 12 and that has to be taken in the context that the numbers are decreasing. And so the AEs are definitely front loaded here. And this does compare it to the control patient population. But, you know, the control population, let's see --

DR. LINDENFELD: Aren't all the controls dead by two to six months?

DR. YOUNG: This is the --

DR. LINDENFELD: They can't have adverse events if they're dead.

DR. YOUNG: Yes.

DR. LINDENFELD: All the controls are dead after a month, right. So you can't really compare adverse events --

DR. KRUCOFF: Well, but if we're comparing, you know we can say it's obviously unsafe after seven months because there are no adverse

events in the control group.

DR. YOUNG: So this was all the patients in the BTT.

DR. KRUCOFF: Okay. So one of the issues, again, as you think of extending the indication to short and long term support is not only the effectiveness issue but the safety.

DR. YOUNG: Correct.

DR. KRUCOFF: And again, having some sort of data with a comparator it would help us understand whether the seven to 12 months, 13 to 24, whether these outer bars -- basically it doesn't look like there are comparators --

DR. YOUNG: Right.

DR. KRUCOFF: -- because they have all expired by then.

DR. YOUNG: Right. And, again, looking at the types of patients that came into the study, these are not the walking wounded kinds of patients. And I might add that it was question about the patients being on inotropes at trial entry. And for BTT to get into the study, if you weren't on an a

balloon pump or some other assist device, you had to be on two inotropes to actually get into the study. And then if you had a balloon pump in place, one inotrope. So that's why there was a 100 percent of both control patients and patients that went to the VAD group that wee on inotropes. There is a difference between Milrinone and dobutamine and whatnot because of the time period. This was not a pretty patient population.

DR. KRUCOFF: Thank you. I'm all done.

CHAIRPERSON LASKEY: Because of the critical importance of the whole issue of relative contraindications that we've been dwelling on here, before we ask Dr. Somberg for his comments, does anybody in the agency review team care to comment/respond/emphasize?

DR. PINA: I'd be happy to. I'd just like to go over some of the points that Dr. Young has been making.

I had personally not seen the data of the individual patients and reversibility, but I would like to point out that some of the patients

that didn't reverse, still got transplanted anyway whether it was creatinine or pulmonary artery. And once more I agree that pulmonary artery systolic is not the best measure of reversibility, rather PDR would be. And it's sure that the surgeons don't like us to inflate the catheters, but we can use PAD to sort of estimate the wedge.

Another point on the conundrum of the patient that comes in with acute myocardial infarction and cariogenic shock, nowadays we use short term bridges for those patients that are available commercially. That's not the patient that you now immediately list for transplant. So times have changed for that acute very ill patient where you don't know what's going to happen to them in the near future. And I think that cariogenic shock is an excellent example of it.

The next point to be made is that insurance companies don't pick who they cover by your criteria. They pick who they cover by outcomes, and that's how they look at who they choose to pay and recommend their patients. They may

want to see the list of your indications and contraindications to transplant, but it's really outcomes that cuts the mustard.

DR. KRUCOFF: Okay. I'm sorry. Then I have one last question. And, Ileana -- well, maybe, and I'll take whoever can answer.

Based on the current labeling for the LVAD is it actually contraindicated based on the current labeling to use the VAD in the setting of a patient who may have relative contraindications such as are listed in these requested extension of labeling?

DR. YANCY: And before you answer, Ileana, I would say I think that is a critical question because we need to understand what it is about the current labeling indication that really necessitates extending it with this additional language?

DR. PINA: My opinion is that the current labeling does allow the discretion of the transplant center to choose to list someone whom they believe will reverse. and I think that's what

we do all the time. You always give that patient the benefit of the doubt and you go ahead and list them.

And we don't make them status 7, Jim, we make them status 2s because they become status 2 nowadays.

Again, explanation for the panel. The patients are LVADs used to stay at status 1s for a while. Now they become status 2 after a month so they're no longer considered critical except for that first month. And we may keep them status for a while. They are gaining time on the list. As status 7 they gain one month total for all the time that they're status 7. So we like to keep them status 2. And, in fact, I think you've shown in your date of reversible, that some of the patients with the higher ponderosity index actually get better because they're probably moving around and exercising and we get them on diets and weight loss programs.

DR. TRACY: Mitch, was your question whether they can be listed or whether the device -- I thought your question was specific to the

regulation on the device. That's my question anyway.

DR. KRUCOFF: My question is based on the current labeling. The current approved labeling for the device. Was it specifically contraindicated to put the device into patients with the creatinine greater than 2.5.

DR. TRACY: Right. And I don't think I heard the answer to that question.

DR. BERMAN: No. No. No, it is not specifically contraindicated that if a patient has any of these relative contraindications that the device may not be used. The label doesn't say that. The label says you may use it, you have it in writing. I don't remember it in my head.

Patients who are candidates for transplant, it's in your panel pack and it's in -- yes it is because --

CHAIRPERSON LASKEY: Well, that is, but can you shed light on whether there are warnings or precautions?

DR. BERMAN: Yes, the whole thing is not

there.

Currently the indication for use is that the LVAS is intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure, the LVAS is indicated for use both inside and outside the hospital. It doesn't say anything about not using it if the patient has PDR over 6 Wood units or creatinine over 2.5. It doesn't say you can't do it.

DR. TRACY: I'm sorry, I'm going to ask it again. What about the section on warnings, precautions and contraindications, which I didn't find in the panel pack?

DR. BERMAN: It's in the panel pack. It should be in the panel pack in the sponsor's SSED from the original indication for use. I'll go find it.

CHAIRPERSON LASKEY: Okay. Cindy, are you happy?

DR. YOUNG: Could I respond to the question that Mitch asked about the

contraindications, because I do think that this is critical and I would agree with Dr. Berman that I think the language as I read it doesn't say its contraindicated. But I would use the term disingenuous. And if you look at the consensus panels, particularly that 1998 consensus panel that Les Miller led, there was a great deal of commentary in there about what listing for heart transplant meant.

To me, unless you're otherwise specifying in a clinical trial of one sort or another, that you are listing a patient for transplantation and are willing to accept an organ when that patient is listed, it becomes a disingenuous act. And whether or not you make the patient status 7 or keep the patient status 1 or 2, and then turn down organs are offered, I think it misses the spirit of what we're trying to do.

The scenario may vary from place-to-place, but even as Ileana explained with a program that might put a patient at status 2 -- there's that commentary. Even if you place a patient status 2

there are some patients that are going to get an offer pretty quick. An AA patient, an AB patient, a small female, for example.

So, yes, that explains why some might do status 7 as opposed to leaving them status 2. So I would characterize the term for better or for worse as disingenuous as contraindicated more than anything. And this labeling does take some evidence that we have, and I stress the word "some" to support the fact that we can rehabilitate the patient to get him at a point where the day an organ became available, then we would accept that organ.

And I think in the packet the indications with the contraindications are listed there, the section was section 3.

DR. KRUCOFF: Under 4 it says warnings and precautions, see warnings and precautions in the final draft labeling information for use.

DR. YOUNG: Yes.

DR. KRUCOFF: I see contraindications, primary --

DR. YOUNG: Right. Check section 4.

Section 4. It's in that section, isn't it? It's attachment 4A that has that expanded list.

CHAIRPERSON LASKEY: We don't have IFU. So could the agency provide that for us, please?

DR. KRUCOFF: Okay. Obviously under contraindications other than the body surface area issue, none of the other relative contraindications that are being requested today --

CHAIRPERSON LASKEY: Yes. The key issue on the table is the warnings and precautions.

DR. KRUCOFF: Right.

CHAIRPERSON LASKEY: So we just need to see that.

DR. KRUCOFF: Thank you.

CHAIRPERSON LASKEY: All right. I'm going to move ahead while we find this information.

DR. BERMAN: Sorry. Could I just have a brief comment from Dr. Oyer on that same question about included or contraindicated? Phil?

DR. OYER: I'm Phil Oyer from Stanford. I'm a cardiovascular surgeon. Conflict statement would say they paid for my trip today. I'm not a

consultant and own no stock in Novacor.

MS. WOOD: Bring the microphone closer. I don't think they can hear you.

DR. OYER: Okay. As far as the conflict statement goes, they did pay for my trip today. I'm not a consultant and own no stock in Novacor, World Heart, although I did at one time serve as a consultant in past years.

With respect then to the business about contraindications in the labeling, it does say you have to be a transplant candidate. Presumably that means at the time. And the whole point we're talking about today, as many of these patients who are in the group two in fact would not be considered transplant candidates at the time. So, you know, I think in actuality it would be a violation of labeling to put patients like this into an LVAD.

And the other point to be made I think as far as listing them status 2, that's probably a fair clear violation of UNOS guidelines if in fact you don't intend to transplant them during, you know, if a donor does become available.

DR. KRUCOFF: All right. But let's stay in focus. Because the fact that those patients were in the BTT trial meant that somebody considered them a transplant candidate. And the fact that somebody else might not consider them a transplant candidate is actually a different issue. In fact, the reality is that the patients who are actually the source of the data being discussed to support this labeling change, were all patients who were enrolled in the BTT trial listed as transplant candidates.

DR. OYER: That's true, they were. But I think we're trying to give the opportunity to patients who might be appear on the doorstep of another center who would not today list those. And even in today's world, many of the patients that we, and Jim certainly talked about at his center, would not really list today for a transplant on the day that we saw them or evaluated them. So that's the whole population I think we're trying to address with this effort today.

CHAIRPERSON LASKEY: We understand that, and we've spent the better part of two hours trying

to articulate exactly who these folks are. So I'd like to just finish up before the lunch hour with Dr. Somberg's review, if you would please, and then we'll break for lunch.

DR. SOMBERG: Thank you, Warren. You put me in a difficult spot being what's between everybody and lunch, but I will try to deal with being in a difficult spot.

I have a detailed review which I will give you a copy of for the record.

I think that it's very important for the panel to realize what it is being asked to give advice on to the division to change the labeling, and what we are being asked to give advice in my estimation are two considerations. One consideration is whether we should change the current wording from an indication to use a device to an indication to use the device both for short and for long; so essentially the addition it for a long term indication.

What do we have to base this on? Well, unfortunately, in the packet given to the reviewers

we have statements to the effect that there is 20 years experience with the device and over 15 implants. But we've heard today, and it was my inclination from a detailed review, that we really do not have information on 15. What we have is a completed BTT trial with the device. And this completed trial compares actually the 35 control patients with the 190 device recipients. And that what we know is today is that while the trial was completed, that it was completed with a control group that preceded from another trial the intervention with the LVAS device group. And that there are a number of severe problems with the control group, as pointed out by the statistical reviewer for the FDA in the package and the presentation today.

The groups are nonconcomitant when there is a lot to give us consideration that being concomitant would be important. Sometimes there isn't in certain studies, sometimes there is. And here there's a lot because there's a constant change in what we do for these patients. So what was done

in '91, '92, '93, '94 is potentially -- not is, but is potentially significant from what was done in '97 and '98 and in the latter part of '96 as well. So that worries me considerably.

There is a number of suggestions in the data, very hard to determine but there is suggestions that the control population was considerably sicker. And that's why there is a 7 day average survival as opposed to the prolong survival in the other population. One can argue well it's the device that makes the difference. But that's to the crux matter, we really don't have anything to support the validity of the control data.

As a reviewer, I would have most appreciated further assistance in this by the sponsor by looking to other publications of control groups in the area. While you only have 35 patients in the BTT trial, there are lots of patients awaiting transplant who never get a transplant who don't have many different interventions of this nature who have received and could be looked at to

substantiate that.

Now, people will say well that's not randomized, it's not appropriate, etcetera. But if I saw that there were five, six, seven groups of 35 patients all with similar outcomes, maybe a little smaller groups, maybe a little larger, that would have swayed me in one way or the other. I saw nothing to support that, and no attempt to do that which I believe is devastating in terms of being able to make a decision on whether long term is adequate.

so what we have here essentially are at the completion of the BTT study with 30 patients for six months and 15 patients for one year, and without a control group to compare them to. We, obviously, know that this device causes a significant number of problems. They're more frequent in the up front than later on in the course of treatment, but we unfortunately don't have anything to base knowing if there is a risk benefit ratio because the control group is so inadequate for comparison.

So, I do not believe, and my detailed

review I believe supports this, is that we have data to extend the indication from what was originally given in terms of approval. And that long term, the data is too small and inadequate control group.

In terms of the bridge to transplant, this is a very interesting concept. It certainly of consider that people with relative contraindications could with some sort of further assistance then become transplant eligible and be appropriate. And I believe the selection of the parameters, as we've already heard, has been done on an arbitrary basis and the numbers of people with each given relative contraindication very small and making the cells very hard to compare. But I do think there are constraining transplant lists and there is tremendous difficulty in deciding who gets a heart and who doesn't for transplant, and thus the concept does sound appealing to me. And I would, unlike some panelists possibly, accept this idea even though it was arbitrary and even though there was little justification presented in the handout for why these considerations were made. However, once

again, there are substantial difficulties with reaching any positive conclusion here.

One is that the control population is now 12. It once against is none nonconcomitant. It once again is inadequate for a comparison and once again we have no further historic controls from any other database to try to validate why we should base this major consideration and recommendation on the data here. So we have no further substantiation.

And finally, the most disturbing conclusion I have to make is there is no evidence from the data that I was presented with to review that implantation of device changes these relative contraindications such that it would be more likely to be able to receive a device. We have survival on transplant outcome compare and that really doesn't tell me very much. It just tells me in 1996 the latter half '97 and '98 that it was more likely if you got the device, to get a heart than it was if you didn't the device in '91, '92, '93 and '94 in this very, very small group.

So, yes, it is of concern to me that the

current labeling does not advise physicians what to do in patients who have in their mind a relative contraindications to transplant in terms of implanting this device. But it also very much concerns me that we do not have the information to recommend to anybody that if you do put in this device, A, B or C will happen and therefore you will have a better, a worse or the same outcome as if you did other things.

So, yes, Doctor it's bad to do harm or it's bad not to recommend something and do harm, but it's also bad to recommend something and do harm as well. So really I think what we have here, unfortunately, is a very reliable device with very little information on how to use it for these two questions we are asked for: Long term therapy and therapy when there's a relative contraindications, arbitrary maybe, but still a relative contraindication to transplant. And, thus, we really can't recommend what we should do.

And that really is a summary of my more details review that I will enter into the record.

Thank you.

CHAIRPERSON LASKEY: Did you have any queries for the sponsor?

DR. SOMBERG: No, I didn't. They have really been addressed.

CHAIRPERSON LASKEY: Great.

Well then, thank you both. Thank you sponsor and FDA.

I suggest we break for lunch. And I'd like to resume at 1:00, it being a quarter to 12:00.

Thank you all.

(Whereupon, at 11:40 a.m. the panel was adjourned, to reconvene this same day at 1:00 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:05 p.m.

CHAIRPERSON LASKEY: Okay. I'd like to reconvene, if we may. And we'll proceed with the open committee discussion. We've already heard comments from Drs. Krucoff and Somberg. And I'd like to just go around the table and give the other panel members opportunities to query the sponsor for things which have not had enough clarification.

In addition, I know the sponsor was asked to provide some material this morning, and they've informed me that they have. So we'll allow a little bit of time for the presentation of that information.

Having said that, if we can being with Dr. Aziz. And I'd like to in the interest of efficiency and keeping us all on schedule, just confine each speaker to ten minutes, and I'll be watching.

Dr. Aziz, thank you.

DR. AZIZ: I'll try to be brief. I'll

try to address most of my questions in the surgical arena and leave the statisticians to quibble over the statistical aspects.

I do realize we have Dr. Oyer over here who I think most of you may not realize I think did the first sort of successful transplant using the Novacor device in '83 or '84. So I think that sort of I think set the stage for these sort of rather terminally sick patients.

Let me ask you a couple of questions, maybe I could ask Dr. Oyer if he doesn't mind coming up to the podium there.

You know, for surgeons who have these patients with elevated pulmonary hypertension, clearly that's one of the risk factors for heart transplantation, in patients in whom you have to put the LVAD either as a bridge or to try to get the pressures down, what is the incidence both in your experience in those patients intra-operatably, for example, having right heart dysfunction or failure?

DR. OYER: Well, over the years we have had very few of those, in fact, with the Novacor

device, at least because it unloads the left side so well, reduces the left pressure so well presumably.

I have I think only in one circumstance put an RVAD in that was a short term biomedic, so I'm not sure how many, probably 75 or 80 over the years. So I think with -- you know, in the earlier days we had other drugs -- you know, nitric oxide wasn't here. We used Prostaglandine E for a while, and it came out in the late '80s or so. But I think we've gotten away in general with managing those patients pretty well. In most cases with drugs over the years we've been able to bring those pressures down so that we've not had to use RVADs except I think one patient.

I think we may have had one other patient die of right heart failure bona fide post-Novacor that we didn't, for one reason or another, put a device on the right side. So it's been fairly limited in our experience, the need for RVADs that is.

DR. AZIZ: I mean, not only in your experience but maybe in the literature, in patients

who have so called fixed pulmonary hypertension.

DR. OYER: Yes.

DR. AZIZ: You know, from what I remember of patients who have elevated PA pressure, I mean I can recall having patients who have been in the ICU for a year using various type agents and eventually the pressures came down. I can also remember putting RVADs in patients who had pulmonary -- with very high PA pressures and putting an RVAD in those patients wasn't very helpful. In fact, you know, you would get bleeding out of the AT tube. So to me it seems that even putting an LVAD in patients who have elevated pulmonary pressures, you're taking a risk. I mean, they're not like you're putting an LVAD who somebody who is just having hematein and they compromise. So you are taking a higher risk group of patients in doing so, and I think it's remarkable that the problems that one sees is not as high as it probably could or should be.

What I see from a surgical point of view, I mean we have really clear indications. You have patients for LVADs who are having hemodynamic

problems and who would be transplant patients without the relatively increased risks. And then you have patients who clearly are contraindications for LVAD; infection or malignancies. But the group in the middle to me that seems to be a moving target. One is the drugs improve; nitric oxidic maybe the receptor blockers, you know, that's really that have been shown to be -- the like help patients with pulmonary hypertension. So this group of patients, I think, where we are not may not be where we will be in two or three years time.

What I'd like -- obviously, you have a great experience in dealing with the high risk patients. And what would you advise centers that don't do a lot of these sort of cases if, let's say, the indication was given that this device should be used in patients who have pulmonary hypertension of variability that hopefully that would be reversible. Do you see centers that don't do many transplants using this for these high risk patients, and do you envision let's say more problems in centers that do that?

DR. OYER: You know, I think at the end of the day it's going to be the judgment of the surgeons at those local centers and cardiologists. I think I agree with you entirely, though, that as time has gone by we've had ore and more drugs that will allow us to separate out which ones are going to have a reactive pulmonary vascular -- from those that don't. Be that as it may, there are still some patients that it's a dilemma and that we can't, you know, get those pulmonary artery pressures down enough to make us comfortable. But I think, you know, certainly if they've got grade 4 pulmonary vascular changes, some of those will not come down. And as we heard from a couple of people today, we can't always predict that. But I think that's not a reason probably to not go ahead. I mean, that problem is no different than the problem that we face with putting an LVAD in in the first place. You can't guarantee that they're not eventually going to fall off the transplant list because of a complication of the LVAD or whatever.

So I don't think that's a unique

problem. And I think if -- you know, and a direct answer to your question, a center with a small number of patients per year and they put in LVADs, assume they've got enough experience to do those. I don't think, you know, a center doing three or four a year and one LVAD every five years is probably appropriate even to be doing LVADs at all, for example. But I think, you know, if assuming they have enough experience putting in LVADs, then I think it's not unreasonable to suggest that in a patient if they encounter that has pulmonary pressures and they can't be comfortable in how well they can get them down if they were to transplant them at that time, then it's not unreasonable to suggest that an LVAD would be appropriate to see. And you saw the data that we have showing that in the majority of cases those pressures do come down one way or another.

DR. AZIZ: I guess there must be some patients where you put the VAD in and the pressures don't come down. I mean, what happens to those patients? Do they become part of so called

destination therapy because they can't be transplanted?

DR. OYER: Well, I hesitate to destination therapy, because that tends to confuse with bone fide destination therapy, patients that need a separate set of criteria. But I think at the end of the day, yes. If we encounter a patient whose resistance has stayed up, then at the end of the day we would not be able to transplant them and they would end up being a long term -- longer term -- whatever the term you want to use would be.

DR. AZIZ: Okay. Thank you.

CHAIRPERSON LASKEY: Thank you.

Dr. Hirshfeld?

DR. HIRSHFELD: I'd like to ask the World Heart representatives to comment on just the context in which this requested indication exists. And in particular, I would like to hear comments about the relationship of this indication requested to the issue of destination therapy.

You indicated that you're embarking on a destination therapy trial now. But it's not clear

to me, and this is what I would like clarified, as to what the role of seeking this indication is in terms of the actual impact on clinical practice if it's not in fact to open the door to people who would ultimately become destination therapy patients?

The reason I ask this, and this is what I would like to comment on, is that it seems that the strict request that you've put in and the strict language is actually well within purview of current accepted clinical practice that patients who are covered under the strict definition of your request are patients who current transplant cardiologists could legitimately decide could have this device implanted in a bridge to transplant mode. And so what I'd like would be for you to clarify the relationship of this request, why this request is important, what it offers the transplant cardiologist and how it relates to the ultimate goal of seeking a destination therapy indication for this device.

MR. BRYDEN: I'd like to respond to part

of that question and then ask Dr. Edwards if he would mind giving you more of the clinical response.

The context of this request is that we filed nearly two years ago a request to the FDA for a PMA for destination therapy based on a Basian based statistical analysis model which included that data from around the world to the extent that there was auditable and reliable data there that included North American data which was outside the trial and it included the bridge to transplant data as well. And after very considerable work with the FDA and work by the FDA, they concluded that they were not satisfied that without a prospective randomized trial that they were prepared to approve an indication for destination therapy.

During the course of that process, however, we concluded that should we be successful in a destination therapy label of exactly the same as the one that is currently -- was then and still is currently in place, that there was a group of patients that following the rules would be neither and analyzed ourselves where will those patients

fit. And it was that that caused us to come back to the FDA rather than simply withdrawing our submission and replacing it with the destination therapy submission that we proposed to the FDA that we would submit a request for and ultimately have receive their conditional approval to proceed with a randomized trial randomizing our product against heart mate for destination therapy. And that we would proceed with a very much more specific request for expanded bridge to transplant indication, which is how this particular request arose.

It is our view and I believe the view of the doctors who are speaking with us today that a significant number of patients who would be or could be assisted as a bridge to transplantation while not yet a candidate are either not receiving a therapy or being listed as a candidate at a time when if a heart were available, it would then not be implanted because the patient is not then in condition to receive it. And while we recognize that the process of deciding who is a candidate is left intentionally by the regulators, both CMS and FDA, to the

individual clinics, once those clinics have established their procedures then the standard that they are held to is that they administer in a consistent manner their own procedures. And in many cases the administration in a consistent manner of the criteria that are established in the transplant clinics would not list a patient who was not at the time of listing ready to receive a transplant.

So our focus is a relatively modest number of patients, but a group of patients who in our view, if and when we are approved for destination therapy, will still require that if they're going to be served it will be by, as Dr. Young observed, being ingenuous; that is either listing them as a candidate when they're not yet truly listable under their own criteria or treating them as destination therapy when the real intention is that after being supported for six months or a year or whatever, they're going to get transplant which is not the intention of destination therapy. And a candidate means someone listed for transplantation.

So that is the basis, the background of this indication. We believe it is material to the patients who it will effect. It is material to us at the margins. It will increase the theoretical population available by some modest number, and of that some share of those may in the next three or four years actually find their way into a device use that would have otherwise not have done so. But it is a gap in our view in the approval process at this moment, and one that we have the opportunity and the data to support.

So that is why we are doing what we're doing, and we by all means intend to pursue as aggressively as we can the reliant trial and expect ultimately to be approved for destination therapy. But it will not capture those patients if they are accurately represented within the rules that most clinics apply to their own selection process.

Dr. Edwards would like to comment further, if you don't mind.

DR. EDWARDS: Thank you very much.

I'm Brooks Edwards. I'm a cardiologist,

Medical Director of the transplant program at Mayo Clinic.

And it's been an interesting morning hearing the discussion. I appreciate the thoughtful consideration that the panel is obviously taking.

As a clinician I'd like to present a view that is really patient centered and not based in statistics. And coming from Mayo, we have a lot of history and adages. And there is one adage from Will Mayo himself that is quoted frequently, and that's "The needs of the patient come first." It may sound trite, but at the end of the day statistics aside and everything aside, that's really how we make decisions; the needs of the patient come first.

The dilemma here is that sometimes the needs of the patient and the labeling indications are at conflict. And what do you do when there's a conflict between the approved indications and the needs of the patient? And we really get back to the old adage: The needs of the patient come first. Ethically we have no other option. But it does put

the physician in a compromised position to propose off-label use of the drug or device for a patient when you really believe that that's the best therapy for your patient.

And what I want to do is quickly tell you about one patient that I've been caring for the last several years, a fellow --

CHAIRPERSON LASKEY: Very briefly, please.

DR. EDWARDS: Okay. Forty-eight years old, my age. He's got a son in middle school, as I do. Severe dilated cardiomyopathy despite aggressive, best practices, all available therapy, he had 16 hospitalizations in the 6 month period. And it was clear to all of us that this fellow was not going anywhere but down and he was going to die. He was an ideal transplant candidate except for one problem, he weighed 315 pounds. And in our center we won't list somebody who weighs 315 pounds.

We could propose destination therapy for him, but that really wasn't what we wanted. What we wanted is bridge to candidacy. We wanted to put a

device in this man to bridge him long enough so that he could lose weight, either with surgery or with conventional weight loss mechanisms. But that's the patient who falls between the cracks with the current indication. He's not a bridge to transplant because he's not a candidate right now. He's not a destination therapy patient, because he's 48 years old and I told him a destination device is not going to let him see his kid graduate from high school. What we really want to do is bridge to candidacy.

And so I think this is the kind of discussion that at the end of the day if you go back to the needs of the patient that's the indication we're looking for.

CHAIRPERSON LASKEY: This body entertains both the clinical needs as well as the scientific needs of the process. So we appreciate your input, but we are clinicians at heart as well. We wear other hats up here.

Dr. Weinberger?

DR. WEINBERGER: I don't have much substantially to add to what's been said, other than

the feeling that what this labeling change will do is basically open the back door to use of the device as destination therapy. And it's very hard for me not to feel that way.

If a patient with a creatinine of 5 who you know and I know is not going to recover would, according to the new labeling indications be eligible for the device. And if three three or six, nine months from now has not turned around, what's that patient supposed to do? Anyone from the sponsor can reply to that?

What is the game plan here for patients who fail to respond to device?

DR. YOUNG: I'm very sensitive to that issue for several reasons. Number one, I'm a big believer in bridge to transport therapies. I think that's where the data gives us the greatest information about success. And I think I'm a qualified believer in destination therapy, given the information that we have and I think things are getting better. But I want to reiterate the comments that this is absolutely in no way to be

construed as trying to open a back door to destination therapy. This is trying to help us clinicians do the best job that we can do for our patient.

And I can tell you that an individual that I knew wasn't ever going to be a candidate for transplantation is not the individual that I would recommend this device put in. So somebody who is a diabetic with chronic renal failure and we know has creatinine clearances that are 30 or less that is heading towards end stage renal disease and all of the implications therein would be looked at quite differently with respect to these devices than would somebody that we feel has flow induced difficulties.

You also alluded to one point that you sometimes can't predict who is going to get better and not. And I share that and I an frustrated by that fact. But this is not an attempt in any fashion to try to get a back door into destination therapy.

We'll have our trial that shows the worthiness of this particular device with destination therapy, and that trial many of us

clinicians are very committed to doing and to completing. And it is not the same thing as this request.

DR. WEINBERGER: But the data that you have, it's hard for me not to get my mind around this, came from heart failure specialists who felt the patients entering were candidates for heart transplantation.

DR. YOUNG: Well, I have to go back again to comments that we had made earlier about the historic time period that these clinical trial, this particular clinical trial was ongoing and the evolution of data that has occurred since that time and the refinement of the process. Not to mention the changes in organ allocation that have occurred and also the divergence from consensus that has developed about many of these patients.

DR. WEINBERGER: So you're saying that back ten years ago patients who were acceptable as heart transplantation candidates are no longer heart transplantation candidates today?

DR. YOUNG: Many times that is the case,

yes. And in other situations many cases that we didn't feel were acceptable for transplantation, we would feel would be acceptable today. And the age criteria I've already addressed a little bit.

But the other thing is, is that I do know as I termed it some disingenuous listing occur. And we know that from data that comes back from the number of refusals that UNOS tallied in individuals where organs are offered but turned down because the patient is in fact too ill.

DR. WEINBERGER: Okay. The last point is a technical point about the trial. When a patient gets a device, that patient is immediately UNOS 1-A or do you want to make him UNOS 1-A until they recover from the operative procedure?

DR. YOUNG: Right now we have three decisions that can be made. We can take 30 days of UNOS 1-A allocation, which we can activate at any time course in the patient's post-VAD placement. That's one choice.

In the patient that has no relative contraindications who the device is going in for

hemodynamic stabilization, we might start the clock ticking the day or two after surgery if everything is okay.

The second choice, as Dr. Pina pointed out, listing the patient as status 2 hoping that you won't get phone calls with organ offers. Or the third choice is making the patient a status 7 where you will not get any offers until you activate the patient as either 1 or 2.

DR. WEINBERGER: What was mandated in the your BTT trial?

DR. YOUNG: Well, none of these because at the time that the BTT trial was ongoing these allocations schemes were different at that time and the standard operating procedure would be to turn down an organ if it were offered if you as the clinician didn't feel the patient was an acceptable candidate at the time.

Unfortunately and one thing that I would have loved to have done, I can't get you information about the patients that are in this clinical trial and the number of organs that were offered and

turned down. What I can say from the UNOS data and also from the transplant advisory committee that has looked at this, that this is a big issue that concern has been raised about.

CHAIRPERSON LASKEY: Dr. Lindenfeld?

DR. LINDENFELD: I have just two questions.

The first is in these relative contraindications I'm having a hard time understanding what the LVAD will change about age to make the patients a candidate for transplant and why that should be on the list?

DR. YOUNG: Well, it won't per se, and as we addressed, unfortunately the device is pretty good but it's not going to last that long to make him regress in his age. But, as you know, age is a multivariable sort of factor. If you have somebody with a creatinine clearance in the 30 to 50 range and the patient is 65, you might look at that patient a heck of a lot different than the patient with a creatinine clearance that's the same, but the age is 40 or 45. So for that reason I think age is

something that should be looked at and should be included, although it is certainly a relative factor, relative of the other things. God forbid that you throw in pulmonary hypertension, diabetes and a few other issues in a 60 or a 65 or 70 year old patient. That 65 year old patient rapidly looks older with all those other things. So that, to me, is why age is still a relative issue.

DR. LINDENFELD: And then a second question which comes to the issue, it's nice to know that the patients with one or more relative contraindications had nearly as many transplants as the total BTT group, 70 versus 65 percent, I think. But I think what's more important to me is that I understand that patients who had a relative contraindication didn't just get the transplant but had a similar survival to the whole group.

DR. YOUNG: Right.

DR. LINDENFELD: So I think what I would like to see is some sort of one and two year data on those two groups about total survival.

DR. YOUNG: Right.

DR. LINDENFELD: And to make sure that the survival that these creatinines don't sort of cause down the line one year problems. And we know pulmonary hypertension leads to -- so do they get transplanted but do they have a substantially worse outcome? Do we have that data? And it's hard for me to evaluate this without seeing that?

DR. YOUNG: We do have that data, and some of it is in the packets. Because the BTT trial, the primary end point as we discussed was 30 day post-transplant survival, we have that data out to 30 days. And we do have one year data out that shows that the survival rates were similar in both the groups.

DR. LINDENFELD: With and without a relative contraindication?

DR. YOUNG: With and without relative contraindications.

DR. LINDENFELD: I think it would be important to see that. If we're going to encourage people to take these marginal patients, we ought to have data that that's a wise thing to do.

DR. YOUNG: Do you have one year data?

DR. LINDENFELD: I mean for the 115 with no relative contraindications and the 75 with one or more?

DR. YOUNG: Right. Yes. We don't have that. We have it for the total, for all of the patients that were followed out --

DR. LINDENFELD: See, I find it -- again, and this is my problem with this problem with this data, but I think it's a critical problem in that we're taking patients who we've said people might be worried about with relative contraindications, and the only data we have that that's okay is that they get to transplant. But we don't know that the one and two year survivals in those groups with and without contraindications are similar. And I would like to be reassured about that.

DR. YOUNG: Well, we can get you one-twelfth of the way.

DR. LINDENFELD: Okay.

DR. YOUNG: At least a one month data.

DR. LINDENFELD: Well, but one month is not -- you know, not all of them have been transplanted even.

And then I guess the other part of a similar question that I have is we saw adverse events for the whole group and we saw that they tailed off early on. But I guess what I'd like to be reassured is that the patients without a relative contraindications and the patients with one or more relative contraindications had approximately the same number of adverse events. In other words, you're taking a high risk group.

DR. YOUNG: Right.

DR. LINDENFELD: And what kind of adverse events, what kind of hospital days do we see in this group with one or more relative contraindications? And I think those two sets of data are critical for me wanting to encourage people to expand the indications.

DR. YOUNG: Right. I think the best answer to that was that one slide that we showed where we took the no relative contraindications and

set that mark at the 100 percent level and then the relative event rates that were occurring up and down with the confidence intervals. The only thing that I can say is that the wide confidence intervals created a nonstatistically significant interaction between those two groups, though numerically as you might suspect, the patients with relative contraindications did have more events. But getting to transplant was equal or seemingly equal. Similar, I guess, would be a better statistical term in the two groups.

DR. LINDENFELD: And I think that's good data, but I still have trouble. If we're going to encourage these potentially marginal candidates, we want to be sure that the ultimate thing we're aiming for, which is transplant --

DR. YOUNG: Long term survival.

DR. LINDENFELD: Post-transplant long term survival is equally as good. And I would think that that data is available. And with that, just how many hospital days, how much bleeding, those kinds of things in the two groups is critical for me

for evaluating this data.

And that's all I have.

MR. BRYDEN: I'm sorry. The data to one year is available. It hadn't been broken out, so we don't have it in a file that we can actually access at this moment. Should there be a view that would result in further discussion with the FDA, we certainly can provide that and can provide it to the panel. But we do not have interactive access to our database back in Oakland that we can do it at this moment. We do have it for 12 months.

With respect to adverse events as well, those were summarized and the details of that summary can also be provided. But the one slide with the summary of adverse events did show that there was no statistical difference, although slightly higher levels of adverse events in the--

DR. LINDENFELD: Well, let me just apologize if I don't recollect that slide properly. That was the differences between the two groups in a whole bunch of different events. It wasn't the sum of all the events together. And I would say that

what you would want, first of all, the serious adverse events and you wouldn't want to just say -- because the numbers are small. One adverse event comparing the two groups is not likely to be statistically significant, but you'd want to pile all those up and say, okay, were serious adverse events substantially more common than the group without a relative contraindications versus those with.

And I think with the numbers you have there's no way that each individual one is going to be different between the two groups. So we need to see a summary of that data.

MR. BRYDEN: Yes.

DR. LINDENFELD: And hospital days would also be, of course, very valuable.

MR. BRYDEN: That is not difficult to do, and we'll be happy to provide that.

CHAIRPERSON LASKEY: I mean, at risk of exaggeration, that is efficacy and safety right there, which is something we desperately need to see.

Dr. Bailey?

DR. BAILEY: I'll try to keep brief here because a lot of points have been discussed.

Obviously, as a statistician it's always nice to see randomized data, and I've heard the arguments that this can't ethically be done. I guess I'd just like to keep that idea alive. If there's any way of changing the end point or some way of thinking harder about that, because I think that's the best way we get good data.

I mean, a lot has been said about the comparability between the two groups here. And it's laudable, you try to do everything you can to adjust for differences, but ultimately one group, the LVAS group one tends to think there may be a healthy volunteer affect if you were doing a clinical trial. With the LVAS group that may well be operating. With the other group, at least there's a subgroup who refuse to get an LVAD. So it isn't that they agreed to accept medical therapy, they refused participation or at least refused the LVAD. Obviously, they had to agree to participate in the

study, I presume. But one is worried that there may be a healthy volunteer effect that's operating in one group and not the other.

I'm sort of beating a dead horse here, obviously. But just to get back to the idea that we need -- and I responded very well to Dr. Somberg's point this is one control group, but once you get away from randomized data, you know, is it enough to just look at one control group. It really behooves us to get every possible other source of data that might be more, perhaps, current in terms of being able to compare these outcomes.

Obviously, again, I'm sort of going over old territory here. But I think it gets to the point that once you've accepted the comparison between the two groups, as Dr. Ahn pointed out, it's going to be very difficult to find a subgroup that does as badly as the control group. So it's sort of a foregone conclusion that you're going to get a significant difference.

So we're left with I think then, okay, how good are the data to allow us to extrapolate the

good outcome in the overall group which were patients who were listed for transplant, but now let's see if we can find a subgroup that really shouldn't have been listed for a transplant and maybe that will allow us to see if this device would work and have similar results in patients that are contraindicated. And I think there then we're being asked to believe that people who slip through the cracks and were actually listed for transplant but happened to have one or more criteria that technically should have kept them from being on the transplant list are equivalent to a group that nobody ever listed for a transplant. And the problem is that the criteria that are violated may be violated more seriously in the people we're trying to extrapolate to than the people who slipped through the cracks, so to speak, into the study.

You can't prove that's true, but what are the different possible explanations for the lack of a gradient in a survival outcome when you start adding these contraindications? Well, one possibility is that the LVAS is so good that it

keeps people alive even that have these contraindications. But another possibility is simply that we don't have enough power because we're so near the fringe here that we don't have really have enough variability of these characteristics to be able to safety extrapolate the results.

So I think we're nervous about extrapolating from people that are sort of on the borderline, on the fringe, to the vast group of people who also have contraindications but maybe they have three or four of them. I mean, just because the words one or more contraindications applies to the group that was studied and the group we're extrapolating to doesn't mean they have the same number of contraindications or that they're violated as severely.

So that's where I get nervous is trying to extrapolate the data. So I guess I'd like to hear more about why it's unethical to do some form of a randomized trial here. Perhaps one could even look at functional status as an end point and have, perhaps, the ability to receive an LVAD as a backup